

REMARKS

Claims 1-28 are pending in the above-identified application.

Claims 1, 7-13 and 22-27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kotula *et al.* (*Biotechnology* 1991;9:1386-1389). According to the Examiner, Kotula and colleagues teach a recombinant yeast cell comprising a non-yeast DNA (mouse IgK gene) wherein the codon bias of the mouse gene is optimized for the expression of the gene in the yeast *S. cerevisiae*; wherein the region having a high content of codons that are poorly suited to yeasts contains at least two poorly suited codons among ten consecutive codons; wherein the replaced codons are in the 5' region of the gene; and wherein the optimized gene is operably linked to heterologous 5' and 3' regulatory elements. According to the Examiner, Kotula *et al.* teach each and every element, and therefore anticipate, Claims 1, 7-13 and 22-27.

Claims 2-6 have been rejected under 35 U.S.C. § 103(a) as being rendered obvious by Kotula *et al.* (*Biotechnology* 1991;9:1386-1389) in view of GenBank "Codon Usage Database" (<http://www.kazusa.or.jp/codon>). The Examiner contends that, as set forth above, Kotula *et al.* teach optimization of codon utilization for enhanced production of heterologous proteins in yeasts, but do not specifically teach which codons should be employed in yeast nor the utilization frequencies of desirable or undesirable codons. However, the Examiner asserts that one of ordinary skill in the art could obtain such information by combining the teachings of Kotula *et al.* with those of the Codon Usage Database.

Claims 15-18 have been rejected under 35 U.S.C. § 103(a) as being rendered obvious by Kotula *et al.* (*Biotechnology* 1991;9:1386-1389) in view of Neill *et al.* (*Gene* 1987;55:303-317). The Examiner contends that Kotula *et al.* teach optimization of codon utilization for enhanced production

NY02:443002.1

of heterologous proteins in yeasts, but do not specifically teach codon optimization of a plant enzyme. The Examiner also contends that Neill *et al.* teach the production of α -gliadin in yeast, but that the yield of α -gliadin production in yeast is limited by the availability of a particular glutamine tRNA. Based on these contentions, the Examiner asserts that one of ordinary skill would have realized that the limitation of α -gliadin production in yeast could be overcome by codon optimization, as shown for a mouse gene by Kotula *et al.* The Examiner therefore concludes that the combination of Kotula *et al.* with Neill *et al.* teach each and every limitation of, and thus anticipate, Claims 15-18.

Claim 27 stands rejected under the judicially-created doctrine of obvious-type double patenting. According to the Examiner, Claim 27, while not identical to Claim 1 of U.S. Patent No. 6,180,363, is not patentably distinct from this latter claim because each describes a generic method of producing a polypeptide in yeast wherein the gene encoding the peptide has undergone codon optimization for expression in yeast, with Claim 1 of U.S. Patent No. 6,180,363 representing a specific limitation of the generic claim of the instant application.

For reasons set forth below, Applicants respectfully request that the rejections be removed and the claims be allowed to issue.

I. The Claims Are Not Anticipated

Claims 1, 7-13 and 22-27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kotula *et al.* (*Biotechnology* 1991;9:1386-1389). According to the Examiner, Kotula and colleagues teach a recombinant yeast cell comprising a non-yeast DNA (mouse IgK gene) wherein the codon bias of the mouse gene is optimized for the expression of the gene in the yeast *S. cerevisiae*; wherein the region having a high content of codons that are poorly suited to yeasts contains at least two

poorly suited codons among ten consecutive codons; wherein the replaced codons are in the 5' region of the gene; and wherein the optimized gene is operably linked to heterologous 5' and 3' regulatory elements. The Examiner concedes that Kotula *et al.* do not teach codon optimization of a plant enzyme for production in a recombinant yeast.

In response, Applicants herein have amended Claims 1 and 9 to more fully and accurately describe the subject matter of the instant invention. Specifically, the claims have been amended to limit the recombinant non-yeast cDNA species covered to those which encode a plant protein of interest. Applicants assert that, in light of these amendments, Kotula *et al.* do not teach each and every element of Claims 1-28 and therefore do not anticipate the claimed invention. Applicants respectfully request that the rejections of Claims 1, 7-13 and 22-27 as being anticipated by the teachings of Kotula *et al.* be withdrawn.

II. The Claims Are Not Obvious

Claims 2-6 have been rejected under 35 U.S.C. § 103(a) as being rendered obvious by Kotula *et al.* (*Biotechnology* 1991;9:1386-1389) in view of the GenBank "Codon Usage Database" found at <http://www.kazusa.or.jp/codon>. Claims 15-18 have been rejected under 35 U.S.C. § 103(a) as being rendered obvious by Kotula *et al.* (*Biotechnology* 1991;9:1386-1389) in view of Neill *et al.* (*Gene* 1987;55:303-317). The Examiner contends that, as set forth above, Kotula *et al.* teach optimization of codon utilization for enhanced production of heterologous proteins in yeasts, but do not teach which codons should be employed in yeast, the utilization frequencies of desirable or undesirable codons, or codon optimization of a plant enzyme. However, the Examiner asserts that one of ordinary skill in the art could obtain such information by combining the teachings of Kotula *et al.* with those of either the Codon Usage Database or Neill *et al.*

As discussed above, Kotula *et al.* do not specifically teach each and every limitation of Claim 1 or the dependent claims 2-6 as presently amended. Nor does Kotula *et al.* teach each and every limitation of Claims 15-18.

Applicants concede that Kotula *et al.* do teach that expression of a mouse protein in *S. cerevisiae* may be achieved through the replacement of certain codons in the mouse gene by "only the most frequently used codons [in yeast] for each amino acid." Kotula *et al.*, p. 1389, column 1, lines 6-7. However, Applicants maintain that Kotula *et al.* are silent with regard to the use of codons other than those most frequently used in yeast. Thus, one of ordinary skill in the art must combine Kotula *et al.* with some other teaching to obtain the invention of Claims 2-6. The Examiner maintains that the Codon Utilization Database constitutes this other teaching. However, Applicants assert that one of ordinary skill, based on the teaching of Kotula *et al.*, would select from the Codon Utilization Database only those codons that are most frequently used in yeast to encode each of the amino acids. There is no teaching from either of these references, either alone or in combination, to classify yeast codon utilization into two distinct categories, *i.e.* those poorly suited to yeasts and those well suited to yeasts. Thus, even in combination, these two references do not render obvious Claims 2-6. It is only through the teachings of the instant specification that one of ordinary skill would appreciate that codons other than those most frequently used in yeast may in fact be suitable for expression of heterologous proteins in yeasts. Applicants therefore respectfully request that the rejection of Claims 2-6 as obvious by the combined teachings of Kotula *et al.* and the Codon Usage Database be withdrawn and these claims, as presently amended, be allowed to issue.

Applicants further note that Kotula *et al.* are silent with regard to the expression of plant genes in yeasts. Thus, one of ordinary skill in the art must combine Kotula *et al.* with one or more other teachings to obtain the invention of Claims 15-18. The Examiner avers that Neill *et al.*

constitutes one other such teaching. However, Applicants maintain that a careful reading of Neill *et al.* indicates that several potential reasons are set forth in this article for the poor production of wheat α -gliadin obtained in yeast, including altered transcription or translation rates, protein or mRNA instability, protein toxicity and codon usage biases. *See* Neill *et al.*, p. 315, left column, lines 4-8. There is no indication from Neill *et al.* as to which of these parameters is likely to be critical in limiting the expression of plant genes in yeast. Moreover, while Neill *et al.* do note that unfavorable codon requirements exist for glutamine, a predominant residue of α -gliadin, their recommended solution is the expression of wheat α -gliadin in naturally-occurring or engineered yeast strains that overproduce glutamine tRNA, not mutagenesis of the α -gliadin gene to optimize codon utilization for expression in yeast. *See* Neill *et al.*, p. 315, right column, lines 12-14. Thus, Applicants maintain that, as a prior art reference, Neill *et al.* fails to meet even the "obvious to try" standard, let alone the higher standard required for an obviousness rejection. If codon optimization had been perceived as an obvious solution to the problem of poor α -gliadin expression, the authors would have proposed it. In light of the foregoing discussion, Applicants respectfully request that the rejection of Claims 15-18 as obvious by the combined teachings of Kotula *et al.* and Neill *et al.* be withdrawn and these claims be allowed to issue.

III. The Rejection of Claim 27 is Obviated by the Filing of a Terminal Disclaimer

Claim 27 stands rejected under the judicially-created doctrine of obvious-type double patenting. According to the Examiner, Claim 27, while not identical to Claim 1 of U.S. Patent No. 6,180,363, is not patentably distinct from this latter claim because each describes a generic method of producing a polypeptide in yeast wherein the gene encoding the peptide has undergone codon

optimization for expression in yeast, with Claim 1 of U.S. Patent No. 6,180,363 representing a specific limitation of the generic claim of the instant application.

Applicants respectfully disagree with this position in light of the amendments made herein to Claim 1, from which Claim 27 depends. However, to further the prosecution of the instant application, Applicants herewith file a Terminal Disclaimer pursuant to 37 CFR § 1.321(c) and compliant with 37 CFR § 3.73(b). Applicants note that the filing of this disclaimer is not an admission of the propriety of the Examiner's rejection of these claims. See *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 USPQ2d 1392. In light of this disclaimer, Applicants respectfully request that the rejection of Claim 27 under the judicially-created doctrine of obviousness-type double patenting be withdrawn and that Claim 27 be allowed to issue.

CONCLUSION

Based on the foregoing remarks and in light of the amendments, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

Applicants believe that no fees other than those associated with the filing of the Terminal Disclaimer are due with this timely response. However, should any fees be required in connection with the filing of this Amendment, the Commissioner is hereby authorized to charge Deposit Account Number 02-4377. A duplicate copy of this communication is enclosed.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

Respectfully submitted,

BAKER BOTTS L.L.P.



Bradley G. Geist
Patent Office Reg. No. 27,551

Rochelle K. Seide
Patent Office Reg. No. 32,300

Alicia A. Russo
Patent Office Reg. No. 46,192

Attorneys for Applicants
(212) 408-2500

Enclosures